IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Attorney Docket No.: 37945-0003

Applicant: Danuta Ewa Irena MOSSAKOWSKA *et al.*

Appl. No.: 09/142,043 Examiner: F. Hamud

Filing Date: December 1, 1998 Art Unit: 1647

Title: FRAGMENTS OF CR1 AND THEIR USE

#30
7/22/02

DECLARATION OF RICHARD ANTHONY GOODWIN SMITH

I, Richard Anthony Goodwin Smith, do hereby declare as follows:

1. I received my PhD. from Oxford University in 1974. I have been involved in the study of proteins for over 25 years. I am an inventor named in the captioned application. I am the co-founder and Chief Scientific Officer of Adprotech Ltd., the assignee of the captioned application. A copy of my *curriculum vitae*, including a list of publications, is attached as Tab 1.

2. I am thoroughly familiar with U.S. Application Serial No. 09/142,043 ("the '043 application"), and I have revlewed the office action dated March 12, 2002. I understand that the examiner has rejected certain claims as anticipated by Fearon *et al.*, PCT publication WO/91/05047 ("Fearon") and certain claims as obvious over Fearon in view of Capon *et al.* , U.S. Patent No. 5,116,964 ("Capon").

3. I am advised that in order to anticipate a claim, a prior art reference must disclose explicitly or implicitly each and every element recited in that claim. If a prior art

reference discloses each and every element of a claim, the claims is said to be anticipated or lack novelty, and therefore is not patentable.

4. I am further advised that if a single prior art reference does not disclose each and every element of a claim, a claim may still not be patentable if the prior art renders the claim obvious. In assessing obviousness, more than one prior art reference can be relied upon to determine obviousness in view of the state of the art. The teachings of a collection of references can be combined to render a claim obvious provided there is some suggestion or motivation to combine the references, and that there is a reasonable expectation of successfully combining the references in order to practice the claimed subject matter.

5. I review Fearon and Capon with these concepts in mind.

6. Fearon discloses the amino acid and nucleic acid sequences for complement receptor 1 (CR1). Figures 1 and 5 of Fearon purport to disclose the entire sequence of CR1. See page 10, lines 11-20 and page 11, lines 15-31 of Fearon. Figure 6 purports to disclose amino acid alignments of the various SCRs (small consensus repeats) contained in CR1. See page 11, line 32 to page 12, line 9 of Fearon. Fearon does not disclose the unique properties of SCR3, much less the properties of polypeptides containing (a) amino acids 6-11 OF SEQ ID NO: 1 of the '043 application and/or (b) amino acids 11-20 of SEQ ID NO: 1 of the '043 application. At most, Fearon discloses an intact SCR3 as part of the larger CR1. I see no teaching or

suggestion in Fearon to obtain, make or use a partial SCR3 sequence that contains one or both of amino acid sequences (a) and (b) mentioned above. Moreover, Fearon provides no reason, much less a methodology, to identify active subregions within SCR3. Accordingly, there is no factual basis to conclude that Fearon anticipates any of the claims in the '043 application

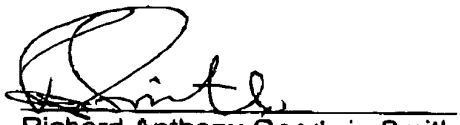
7. Capon concerns hybrid immunoglobulins. More specifically, Capon discloses a "ligand binding partner" fused to the constant regions of an immunoglobulin. See Capon at column 10, lines 1-9. Exemplary ligand binding partners include lymphocyte cell surface glycoprotein (LHR). See column 8-9 of Capon. Notably, CR1 is not mentioned in Capon. Capon seeks to extend the *in vivo* plasma half-life of the ligand binding partner, namely LHR. See column 5, lines 13-21.

8. Capon does not modify Fearon in any sense that is meaningful to the invention of the captioned application. Capon focuses on modifying LHR by fusing it to an antibody fragment. Both of these protein constituents (LHR and an antibody fragment) are wholly distinct from CR1, SCR3 and subregions thereof. Thus, Capon provides the skilled person with absolutely no reason, suggestion or motivation to modify Fearon's disclosure of whole CR1. Simply put, Fearon and Capon are inapposite to each other, and therefore there is no reason to combine their teachings. In any event, even if the teachings are combined in the manner the examiner attempts, there is no disclosure of polypeptides containing (a) amino acids 6-11 OF SEQ ID NO: 1 of the '043 application and/or (b) amino acids 11-20 of SEQ ID NO: 1 of the '043

application. Therefore, there is no disclosure in the combined references of a chimeric polypeptide comprising a host protein with an SCR3 derivative polypeptide having only a partial SCR3 sequence. The SCR3 derivative polypeptide comprises a 6 to 23 amino acid portion of SEQ ID NO: 1 and has (a) amino acids 6-11 of SEQ ID NO: 1 and/or (b) amino acids 11-20 of SEQ ID NO: 1. Accordingly, there is no factual basis to conclude that Fearon and Capon render obvious any of the claims in the '043 application.

I declare further that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements and the like are made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of this application or any patent issuing thereon.

12 July 2002
Date



Richard Anthony Goodwin Smith

BRIEF *CURRICULUM VITAE*

Richard Anthony Godwin Smith

Born: 4 April 1949, Stroud, England - British Citizen
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Education:

Keble College, Oxford University	1967-1973
Batchelor of Arts	- 1970
Part II Honours (Chemistry)	- 1971
Thesis: Fluorinated triose phosphates	
European Molecular Biology Organization training course (Cambridge University)	- 1971
Doctor of Philosophy (Oxford University)	- 1974
Thesis: Photogenerated labels for biological receptor sites	

Employment:

Demonstrator in Organic Chemistry, Oxford University	1971-1972
Beecham Pharmaceuticals Research Division	1974-1988
- enzymologist	
- senior scientist, fibrinolysis research	
- chief biochemist, thrombosis project	
- manager, modified proteins, biotechnology dept	
SmithKline Beecham plc, biopharmaceutical R&D	1989-1996
- director, Protein Chemistry	
SmithKline Beecham plc, molecular screening technologies	1996-1997
- director. Therapeutic Proteins	
Adprotech Ltd, co-founder & chief scientific officer	1997-

Scientific achievements:

- novel penicillin transformation processes	1974-1976
- mechanistic studies on clavulanic acid	1976
(----→ antibiotic 'Augmentin')	
- acyl-enzyme approach to thrombolytic therapy	1975-1980
(----→ thrombolytic 'Eminase')	
- structural studies on fibrinolytic proteins	1987- 1996
- development of soluble CR1 as a therapeutic agent	1989-1994
- structure of IL-4 & fibronectin binding proteins	1992-1994
- membrane addressins & their therapeutic applications	1996- present
- development of novel inhibitors of complement activation	1997- present
- development of C3d-based immune adjuvants	1997- present

(Scientific publications: see below)

Prizes & awards: biochemistry prize (Oxford 1969), Queen's Award for Technological Achievement (1991), Prix Galien (1991)

Scientific interests: protein engineering, integrative molecular biology of adhesion, hemostasis/fibrinolysis, complement activation and inflammation, vaccine development

Publications

This is not a comprehensive list of publications. It is a selection of higher-impact papers designed to illustrate areas of past and present scientific interest and expertise.

1. Photoaffinity Labelling, General Protein Chemistry and Protein Engineering

Smith RAG, Knowles J R. Aryldiazirines: potential reagents for photolabeling biological receptor sites. **J Amer Chem Soc** 1973 95 5072-5073

Smith RAG, Knowles J R. The utility of photoaffinity labels as mapping reagents: a study of sub-populations of a specific rabbit antibody by using structurally related photoaffinity reagents. **Biochemical J** 1974 141 51-56

Smith RAG, Knowles J R. The preparation and photolysis of 3-aryl, 3-H diazirines. **J Chem Soc** 1975 (Perkin Trans.II) 686-694

Significance: these papers are the first describing the use of diazirines as photolabels and also outline photoaffinity labelling methods since widely applied.

Garman A J, Smith RAG. The chemical modification of proteins (review). **Royal Society of Chemistry Specialist Periodical Reports,** Amino Acids, Peptides and Proteins 1982 13 70-131 Also reviewed in vols 14-16 of this series (1983-5)

Smith RAG, Dewdney JM, Fears R, Poste G. Chemical derivatization of therapeutic proteins. (review). **Trends in Biotechnology** 1993 11 397-403

Dodd I, Smith RAG *et al* (6 authors). Isolation and folding of proteins containing the short consensus repeat motif from an *E.coli* overexpression system. **Perspectives in Protein Enginering and Complementary Technologies** (Mayflower Press 1995)

2. Enzyme Immobilisation

Smith RAG. Amphipathic enzyme-polymer conjugates. **Nature (London)** 1976 262 519-520

Smith RAG. The preparation and properties of amphipathic enzyme-polymer conjugates. **Biochemical J**. 1979 181 111-118

3. Fibrinolysis - General

Smith RAG, Green J, Kopper P H. The purification and properties of a fibrinolytic neutral metalloendopeptidase from *Streptococcus faecalis*. **Arch Biochem Biophys** 1980 202 629-638

Dupe R J, English P D, Smith RAG, Green J. The evaluation of plasmin and streptokinase activator complexes in a new rabbit model of venous thrombosis. **Thrombosis and Haemostasis** 1981 46 528-534.

English P D, Smith RAG, Dupe R J, Green J. The thrombolytic activity of streptokinase in the rabbit. **Thrombosis and Haemostasis** 1981 46 535-537

Garman, A J, Smith RAG. The binding of plasminogen to fibrin: evidence for plasminogen-bridging. **Thrombosis Research** 1982 27 311-320

Fears R, Hibbs MJ, Smith RAG. Kinetic studies on the interaction for streptokinase and other plasminogen activators with plasminogen and fibrin. **Biochemical J** 1985 229 555-558

Smith RAG. An active-site titrant for human tissue-type plasminogen activator. **Biochemical J** 1986 239 477-479

Dodd I, Mitchell DL, Chapman CG & Smith RAG. The use of bovine fibrin-streptokinase films for the determination of recombinant human plasminogen. **Biologicals** 1992 20 197-202.

Signficance: these studies contributed to the methodological basis for the development of a new generation of thrombolytic agents.

4. Acyl-Enzyme Thrombolytics and APSAC (anistreplase)

Smith RAG, Dupe R J, English P D, Green J. Fibinolysis with acyl-enzymes: a new approach to thrombolytic therapy. **Nature (London)** 1981 290 505-508

Smith RAG, Dupe R J, English P D, Green J. Acyl-Enzymes as thrombolytic agents in a rabbit model of venous thrombosis. **Thrombosis and Haemostasis** 1982 47 269-274

Staniforth, D H, Smith RAG, Hibbs M J. Streptokinase and anisoylated streptokinase.plasminogen complex: their action on haemostasis in human volunteers. **European J Clinical Pharmacology** 1983 24 751-756

Green J, Dupe R J, Smith RAG, Harris G S, English P D. Comparison of the hypotensive effects of streptokinase-human plasminogen activator complex and BRL26921 (p-anisoylated streptokinase.plasminogen activator complex) in the dog after high-dose bolus administration. **Thrombosis Research** 1984 36 29-36

Dupe R J, English P D, Smith RAG, Green J. Acyl-enzymes as thrombolytic agents in dog models of venous thrombosis and pulmonary embolism. **Thrombosis and Haemostasis** 1984 51 248-253

Dupe R J, Green J, Smith RAG. Acylated derivatives of streptokinase.plasminogen complex as thrombolytic agents in a dog model of aged venous thrombosis. **Thrombosis and Haemostasis** 1985 53 56-59

Fears R, Green J, Smith RAG, Walker P. Induction of a sustained fibrinolytic response to BRL26921 *in vitro*. **Thrombosis Research** 1985 38 251-260

Cassels R, Fears R, Smith RAG. The interaction of plasminogen activators and their acylated derivatives with fibrin and cyanogen bromide fragments of fibrinogen: relationship to fibrinolytic potency in vitro. **Biochemical J** 1987 247 395-400

Smith RAG. The non-exchange of streptokinase from anisoylated plasminogen.streptokinase activator complex and other acylated plasminogen activator complexes. **Drugs** 1987 33(3) 75-79

Hibbs M J, Fears R, Ferres H, Standring R, Smith RAG. Determination of the deacylation rate of p-anisoyl plasminogen.streptokinase activator complex (APSAC, Eminase) in human plasma, blood and clots. **Fibrinolysis** 1987 2 235-240

Smith RAG. Fibrinolysis with acyl-enzymes (review) in **Atheroma and Thrombosis** (ed V V Kakkar) Pitman Press London 1985 269-284

Green J, Harris G S, Smith RAG, Dupe R J. Acyl-enzymes: a novel class of thrombolytic agents (review) in **Thrombolysis: Biological and Therapeutic Properties of New Thrombolytic Agents** (ed D Collen et al) Churchill Livingston Edinburgh 1985 124-167

Significance: these papers describe the conception, pharmacology, pharmaceutical development and first clinical studies on the marketed thrombolytic agent anistreplase (Eminase).

5. Third Generation Thrombolytic Agents

Kalindjian S B, Smith RAG. Reagents for reversible coupling of proteins to the active centres of fibrinolytic enzymes. **Biochemical J.** 1987 248 409-413

Cassels R, Smith RAG. Preparation and properties of a conjugate of immunoglobulin G with the active centre of human tissue-type plasminogen activator. **Fibrinolysis** 1987 2 1889-195

Smith RAG, Esmail A F. Pharmacokinetic properties of a conjugate of tissue plasminogen activator linked through the active centre to human fibrinogen. **Fibrinolysis** 1988 2 (supp 1) 31 (abstract)

Ferres H, Smith RAG et al (7 authors). Synthesis and Fibrinolytic properties of a conjugate of urokinase with the active centre of human plasmin. **Fibrinolysis** 1988 2 (supp 1) 64 (abstract)

Robinson J H,.. Smith RAG *et al* (14 authors). A recombinant chimeric enzyme with a novel mechanism of action leading to greater potency and selectivity than tissue-type plasminogen activator. **Circulation** 1992 86 548-552

Wilson S,... Smith RAG *et al* (9 authors). The use of active central acylation to control the pharmacokinetic profile of a recombinant chimeric plasminogen activator. **Thrombosis and Haemostasis** 1993 70 984-986

Lijnen H R, Smith RAG, Collen D. Functional properties of p-anisoylated plasmin-staphylokinase complex. **Thrombosis and Haemostasis** 1993 70 326-331

Significance: these were further contributions to the design and evaluation of novel recombinant, engineered or other thrombolytic enzymes designed to combine the best features of the currently used agents .

6. Protein Structure Studies

Oswald R E, Bogusky M J, Bamberger M, Smith RAG, Dobson C M. Dynamics of the multidomain fibrinolytic protein urokinase from two-dimensional NMR. **Nature (London)** 1989 337 579-582

Bogusky M J, Dobson C M, Smith RAG. Reversible independent unfolding of the domains of urokinase monitored by 1H NMR. **Biochemistry** 1989 28 6728-6735

Nowak U K, Li X, Teuten A J, Smith RAG, Dobson C M. NMR studies of the dynamics of the multidomain protein urokinase-type plasminogen activator. **Biochemistry** 1993 32, 298-309.

Li X, Smith RAG, Dobson C M. Sequential NMR assignments and secondary structure of the kringle from urokinase. **Biochemistry** 1992 31 9562-9571.

Li X, Bokman A M, Llinas M, Smith RAG, Dobson C M. Solution structure of the kringle domain from urokinase type plasminogen activator. **J. Mol Biol.** 1994 235 1548-1559

Teuten A J, Smith RAG, Dobson C M. Domain interactions in human plasminogen studied by proton NMR. **FEBS Letters** 1991 278 17-22

Redfield C,.. Smith RAG *et al* (7 authors). Secondary structure and topology of human interleukin 4 in solution. **Biochemistry** 1991 30 11029-11035

Smith L J, ..Smith RAG *et al* (7 authors). Human interleukin-4: the solution structure of a four-helix bundle protein. **J Mol Biol** 1992 224 899-904

Redfield C, Boyd J, Smith L J, Smith RAG, Dobson C M. Loop mobility in a four-helix bundle protein: 15-N NMR relaxation measurements on human interleukin-4. **Biochemistry** 1992 31 10431-10437

Redfield C, Smith RAG, Dobson C M. Structural characterisation of a highly-ordered 'molten globule' at low pH. **Nature Structural Biology** 1994 1 23-29

Significance: contributions to structural understanding of proteins of therapeutic importance.

7. Complement Research

Dupe R J, Smith RAG *et al* (8 authors). Utility of complement inhibition during myocardial reperfusion: pharmacology of soluble complement receptor 1. **Thrombosis and Haemostasis** 1991 65 (6) 695 (abstract).

Gibb A L, Freeman A M, Smith RAG, Sim E. The interaction of soluble human complement receptor type 1 (sCR1, BRL55730) with human complement component C4. **Biochimica et Biophysica Acta** 1993 1180 313-320

Dodd I,...Smith RAG et al (9 authors). Overexpression in *Escherichia coli*, folding, purification and physicochemical characterisation of the first three short consensus repeat modules of human complement receptor Type-1. **Protein Expression & Purification** 1995 6 727-736

Mossakowska D, Dodd I, Pindar W, Smith RAG. Structure-activity relationships within the N-terminal short consensus repeats (SCR) of human CR1 (C3b/C4b receptor). **Eur J Immunol**. 1999 29 1955-1965

Pratt JR.....Smith RAG et al (5 authors). Effects of complement inhibition with soluble complement receptort-1 on vascular injury and inflammation during renal allograft rejection in the rat. **Am.J.Pathol.** 1996 149 2055-2066

Bright JR..Smith RAG et al (6 authors). Complement C4 structure. **Perspectives on Protein Engineering** 1993 3 p 6

Dong J.....Smith RAG et al (5 authors). Strategies for targeting complement inhibitors in ischaemia/reperfusion injury **Mol. Immunol.** 1999 36 957-963

Linton SM....Smith RAG et al (6 authors). Therapeutic efficacy of a novel membrane-targeted complement regulator in antigen-induced arthritis in the rat **Arthritis & Rheumatism** 2000 43 2590-2597

Smith GP & Smith RAG Membrane-targeted complement inhibitors **Mol.Immunol,** 2001 38 249-255 (*review)*

Signficance: engineering and evaluation of complement proteins, two of which have entered clinical trials

8.Science Management

Dewdney JM, Smith RAG Putting a new spin on R&D assets in the pharmaceutical industry. **Drug Discovery Today** 1998 3 353-354 (*editorial)*